REMARKS

The Official Action dated December 19, 2000 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place this application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 1 and 28 are amended in accordance with the teachings of the specification at page 5, lines 4-8 and 33-35, respectively. Claim 30 is added, support for claim 30 being found in original claim 1 and the specification at page 5, lines 4-8 and page 12, line 22- page 13, line 7. A Version With Markings Showing Changes Made is attached. Since these changes do not involve any introduction of new matter, entry is believed to be in order and is respectfully requested.

Claim Rejections – U.S.C. §102(b)

Claims 1-3, 5, 6 and 16 were rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 3,870,790 to Lowey et al. The Examiner asserted that Lowey teaches a pharmaceutical composition that comprises a combination of ethylcellulose and hydroxypropyl methyl cellulose together with any pharmaceutical active.

This rejection is traversed, and reconsideration is respectfully requested. More particularly, as defined by claims 1 and 30, the invention is directed to a controlled release pharmaceutical composition comprising, inter alia, a first intelligent polymer component and a second intelligent polymer component having opposite wettablity characteristics to the first intelligent polymer component, wherein the second intelligent polymer component comprises hydroxyethylcellulose (HEC) or a mixture of hydroxyethylcellulose and hydroxypropyl

methylcellulose (HPMC). Applicants find no teaching or suggestion by Lowey relating to a controlled release pharmaceutical composition as defined by claim 1 or claim 30.

Anticipation under 35 U.S.C. §102 requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). In view of the failure of Lowey to disclose each element of claims 1 and 30, Lowey does not anticipate the claimed controlled release pharmaceutical compositions. It is therefore submitted that the rejection under 35 U.S.C. §102 based on Lowey has been overcome. Reconsideration is respectfully requested.

Claim Rejections – U.S.C. § 103(a)

Claims 1-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over Lowey et al in view of U.S. Patent No. 5,162,117 to Stupak et al. The Examiner relied on the teachings of Lowey cited in the previous rejection and relied on Stupak as disclosing conventional excipients. The Examiner asserted that since polymers such as hydroxypropyl methylcellulose and hydroxyethylcellulose act so similarly, they are interchangeable in a pharmaceutical composition and thus it would have been obvious to one of ordinary skill in the art to use one or the other or a mixture of the two hydrophilic polymers.

This rejection is traversed and reconsideration is respectfully requested. The combination of the teachings of these two cited references does not suggest the presently claimed invention. Neither Lowey or Stupak suggest the combination of polymers as recited in present claim 1, or the advantages thereof provided in the claimed controlled release pharmaceutical compositions. Therefore, the combination of Lowey and Stupak do not render obvious the invention as recited in the present claims.

While many ingredients are common in different types of pharmaceutical formulations, it is the specific combination in a relative amount that may provide for altered biological characteristics of the pharmaceutical product. The Applicants have surprisingly found that the presently claimed combination as recited in claim 1 provides for sustained therapeutic effects for over 24 hours with only a single dose and without any food effect. The presently claimed invention is also easy and inexpensive to manufacture and more efficient in providing a sustained release of pharmaceutical agents than known controlled delivery systems. Neither Stupak's nor Lowey's compositions provide for sustained release of an active ingredient for over 24 hours with a single dose. This is an unobvious advantage of the presently claimed compositions not realized by the prior art.

The presently claimed invention is not merely a combination of the cited references since the cited references when combined do not teach or suggest the elements as recited in the claims, or the improvements provided thereby, namely a resultant pharmaceutical composition that has extended release characteristics over a 24 hour period with a single dose.

Specifically, Stupak teaches a delayed release solid dosage tablet designed to provide an immediate release dose and a second delayed dose in pulsatile manner in the GIT for twice a day use. The Stupak tablet is made up of three sections, i.e., an inner core containing a rapidly dissolving solid dispersion of drug, a barrier made of enteric material to provide gastric resistance and delay the drug in the core from being dumped in the gastric juice, and finally a layer of drug applied to the coated core. When the Stupak tablet reaches the GIT, there is an immediate release or dumping of 20% to 80% of drug particularly in the gastric juice, and a second dose is dumped in the intestine. According to Stupak, 60% of the drug is dissolved in 2 hours and 100% is dissolved in 4 hours in a typical in-vitro dissolution profile of a delayed

release product. Furthermore, Stupak teaches the use of a super disintegrant (sodium croscarmellose) in the composition. Super disintegrants are known to disrupt the structure and integrity of a tablet to allow for rapid release or dumping of the drug content.

Lowey teaches the use of the hydroxypropylmethyl cellulose (HPMC) alone for oral tablets as shown in the examples or a combination of hydroxypropylmethyl cellulose (HPMC) and ethylcellulose (EC) for long acting troches, lozenges and tablets. Lowey teaches drug release from 1-8 hours, which implies that the disclosed products will have to be administered about three times a day to obtain 24-hour coverage. Lowey teaches the use of a humidified HPMC together with EC with moisture content as high as 25% as the carrier agent. Such high levels of moisture content are deliberately introduced by Lowey by spraying the carrier mixture with a 35% ethanol/water mixture and also keeping the carrier agents overnight in a steam room or an oven chamber under conditions of high humidity (70% - 90%). According to the teaching of Lowey, it is important to attain moisture levels (20% - 25%) in the blend as this is important to the ultimate performance of the tablet. Lowey teaches that by controlled variation of the moisture content of the HPMC-EC carrier powder, the duration of the release period (1-8 hours) of the active medicament may be controlled. The release of active medicament according to Lowey is also dependent on compression forces used during compression. Lowey emphatically concludes that "release of active ingredient is, therefore controlled by the size and weight, moisture content and degree of compression pressure exercised on the lozenges, suppository or tablet at the time it is being formed from the pre-wetted powder and active medicament" (column 2, lines 49-54). Hydration or moisture content is so important in Lowey's invention that Lowey teaches the use of adjuvants that do not tend to dehydrate the product before or after tableting.

In contrast, the presently claimed compositions comprise a pharmaceutically active substance and a combination of a first intelligent polymer component and HEC or a mixture of HEC and HMPC, preferably with a moisture content of less than 3% as recited in claim 30, without the need for a pre-wetted carrier. The release of active medicament from the present invention is independent of compression forces used for tableting. Adjuvants that tend to dehydrate the product can be used in the present composition before or after tableting. Furthermore, in the present invention, 100% of the active composition is released in 24 hours, demonstrating an extended release product. The composition as a tablet is a single monolithic and homogeneous structure of drug and polymers. The encasement coating of pH reactive polymers may optionally be employed in the composition to prevent a food effect and is not for delayed release.

The mere fact that prior art can be modified to result in a claimed invention would not have made the modification obvious unless the prior art suggested the desirability of the modification, *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Applicants find no suggestion in either Lowey or Stupak for modifying their teachings along the lines of the present invention, and particularly Applicants find no teaching, suggestion or recognition in either reference that a combination as set forth in claims 1 and 30 can provide a controlled release composition providing release over a 24-hour period.

Thus, the combination of the teachings of the references does not suggest to one skilled in the art that such specific elements of each reference may be combined to provide the presently claimed invention. Furthermore, there is no teaching in any of the cited references which would lead one skilled in the art to expect that any such combination of selected teachings would lead to a successful extended release formulation as presently claimed. For these reasons, claims 1-30

cannot be considered to be obvious in view of the combined teachings of the cited art. It is therefore submitted that the controlled release pharmaceutical compositions defined by claims 1-30 are nonobvious over and patentably distinguishable from the combination of Lowey and Stupak, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

In the Office Action Summary included in the Official Action, the Examiner did not acknowledge priority under 35 U.S.C. §119. It is therefore requested that the priority be acknowledged and the Examiner indicate that the certified copy of the priority document has been received.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§ 102 and 103, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

Holly D. Kozlowski
Reg. No. 30,468
Attorney for Applicants
1900 Chemed Center
255 East Fifth Street
Cincinnati, Ohio 45202
Tel: (513) 977-8568
Fax: (513) 977-8141

659001.01

VERSION WITH MARKINGS SHOWING CHANGES MADE

1. (Amended) A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle () such that cos is between +0.9848 and -0.9848;

(b) a first intelligent polymer component; and

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising hydroxyethylcellulose or a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight, the polymer components being effective for controlled release of said pharmaceutically active substance from said composition.

28. (Amended) The composition of claim 1, wherein the pharmaceutically active substance is selected from the group consisting of nifedipine, glipizide, diltiazem hydrochloride, bupropion, buspirone hydrochloride, [Tramadol] tramadol hydrochloride and verapamil HCl.